Experimental Observations on the Influence of Hypothermia and Autonomic Blocking Agents on Hemorrhagic Shock*

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AS A RESULT of the pioneer work of Bigelow,[8–11] the efficacy of general body hypothermia in obviating the ischemic consequences of acute circulatory interruption has been widely documented.[2, 13, 18, 19, 22, 24, 25, 47, 50, 51, 54, 55, 61, 64, 67, 68] More recently the concept has been advanced of the state of "artificial hibernation," mediated by the combination of hypothermia and certain autonomolytic drugs, in which the organism is believed to be resistant not only to acute total ischemia, but also to the wide range of nocuous stimuli which lead to traumatic and hemorrhagic shock.[6, 7, 14, 16, 17, 23 26, 37, 38, 40, 41, 43–46, 49, 66, 70] Broad claims have been made, particularly by French investigators, for this concept and its clinical applications, extended even to its administration to battle casulties in Vietnam.[15, 39, 46, 52] Their method involves use of body cooling, together with a "lytic cocktail" of certain drugs, of which chlorpromazine seems to be the most important.[27] Highly significant as the French work may be, the picture is obscured by the polytherapy employed. It seemed important, therefore, to investigate the problem by a carefully controlled study directed toward ascertaining the significance of the various factors involved in the French protocol.

Because of considerable experience in the study of "irreversible" hemorrhagic shock by the method of Fine,[30, 35] it was considered desirable to employ this shock preparation and to investigate the effects of hypothermia alone, Chlorpromazine alone, and a combination of these two factors on the course of the shock experiment.

METHOD

The procedure employed in the production of shock was essentially similar to that previously described.[35] Healthy, afebrile mongrel dogs, averaging 14.5 Kg. in weight, were bled *via* the femoral artery into an elevated reservoir adjusted at such a height that the blood pressure equilibrates at 30 mm. Hg. The bleeding volume reached a maximum usually in about one hour; thereafter, as the animal's compensation failed, blood was gradually and spontaneously "taken back" in order to maintain the blood pressure at 30 mm. Hg. After 40 per cent of the maximum volume had thus been taken back, the remainder was rapidly retransfused. If this "40 per cent end-point" was not reached in eight hours, the experiment was arbitrarily terminated by retransfusion. Although after retransfusion the animals appeared temporarily improved, in our experiments the mortality from this shock preparation has averaged over 90 per cent. In addition to the survival rate, the dog's response to the experiment and to any therapy employed was gauged by the maximum bleeding volume in milliliters per kilogram, and also by the duration of hypotension necessary to attain the end-point.

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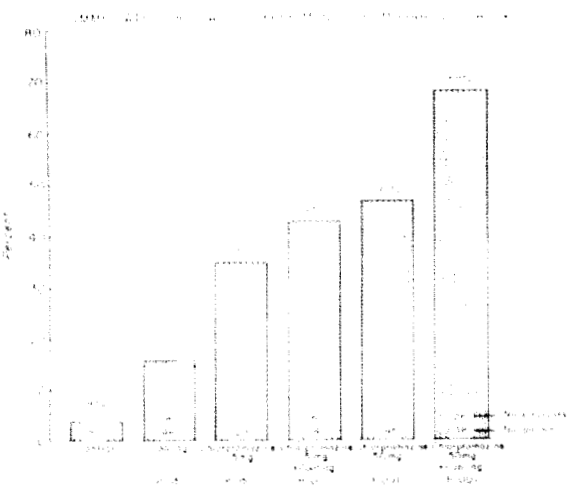

FIG. 1

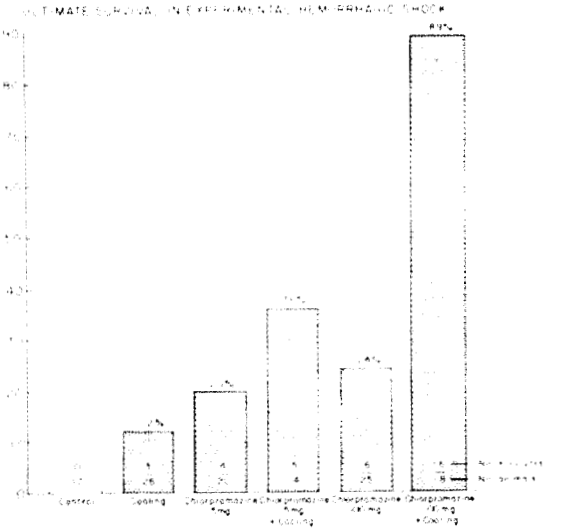

FIG. 2

In both Fine's original work and our previous studies, a local anesthetic was used. In the present study, because of the hypothermia and the necessity for obviating shivering, general anesthesia induced with morphine sulphate (10 mg./Kg.) and pentobarbital (15 mg./Kg.) intravenously was employed. It was realized that this might increase the stress of the procedure, but the factor was kept constant by its application to all animals, including the control dogs. The tracheas were intubated perorally, but insufflation was not employed. The anesthetized animals were wrapped in rubberized blankets, through which refrigerated fluid was circulated until their temperature reached 31° C. Parallel controls were treated identically except for the cooling. Chlorpromazine was given in dosages of 50 and 100 mg. intramuscularly one to two hours before bleeding to one group, and in 5 mg. doses to another. The difference in 50 mg. and 100 mg. dosage has no statistical significance, both being large doses for the dog. Parallel controls were treated identically except they were not given the drug. In the series receiving combined therapy, Chlorpromazine was administered in dosage of 50 mg. approximately one hour before initiation of cooling, and on the average approximately two hours before the beginning of the bleeding to one group, and in 5 mg. doses to another.

The experiment was performed on 46 dogs with hypothermia alone, 45 dogs with 50 mg. of Chlorpromazine, 20 dogs with 5 mg. of Chlorpromazine, 38 dogs with combined Chlorpromazine (50 mg.) and hypothermia, 14 dogs with combined Chlorpromazine (5 mg.) and hypothermia, and 50 control dogs. Slight (1 to 2° C) cooling was secured by the autonomolytic drug alone, and cooling was achieved somewhat faster in the dogs receiving the drug before the application of surface cooling. The discrepancy in number of controls is due to the simultaneous use of one control to parallel one or more of the other groups.

RESULTS

Originally the survival period was arbitrarily determined at the end of 24 hours, since the majority of deaths occurred well within this time. Most of the controls expired at or soon after the end-point. Subsequently it seemed desirable to determine ultimate survival, based upon a minimum period of two weeks. Accordingly the experiments were repeated on additional groups of animals for this purpose. Certain studies carried out in the first groups were

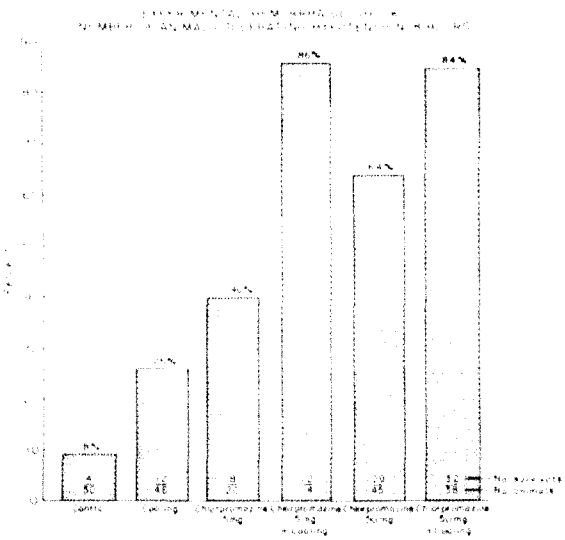

FIG. 3

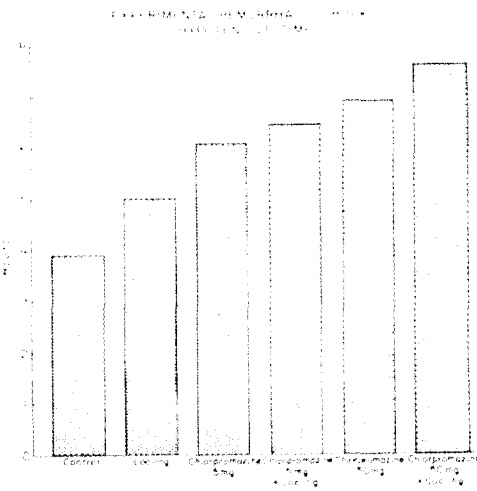

FIG. 4

also repeated in the second groups, thus providing additional data.

Both the immediate, as well as the ultimate, survival rates were increased in all of the experiments as compared with the control animals (Figs. 1 and 2). As might be expected the ultimate survival rates were somewhat less, except for one group of animals, than the immediate survival rates, since in the former groups a number of variables are introduced, such as bacterial contamination and lack of supportive measures. In this connection it has been observed in another experiment conducted in our laboratory that the combined use of anesthesia and hypothermia alone is followed by a mortality of 10 per cent when antibacterial therapy is not employed.[20]

The high proportion of rapid deaths in the control dogs, which is slightly greater than that obtained in our previous studies, testifies to the severity of the stress. Although there was a significant increase in survival rate among the dogs that were cooled before being bled, and an even greater increase in those receiving Chlorpromazine in both large and small doses prior to the experiment, the dogs treated by the combined use of hypothermia and Chlorpromazine in large doses showed the most pronounced increase in survival. The combined use of hypothermia and small doses of Chlorpromazine resulted in a survival rate greater than that following use of the drug alone in comparable dosage, but slightly less than when used alone in larger doses. These results are valid statistically at "p" values of $<.05$, $<.05$ and .001, .01, respectively.

A protective mechanism is also suggested by the increased tolerance to duration of hypotension, or duration of shock, before the 40 per cent end-point was reached. Whereas in only 8 per cent of the control animals was the blood pressure maintained at 30 mm. Hg for eight hours without having to retake 40 per cent of their maximum bleeding volume, among the treated animals this figure was significantly greater. Particularly striking in this connection is the high proportion of "tolerance" hypotension among those treated by the combined use of hypothermia and Chlorpromazine (Fig. 3). At arbitrary completion at eight hours the control animals were 61.8 per cent short of the 40 per cent end-point, whereas the hypothermic dogs were 40.3 per cent, the 5 mg. Chlorpromazine-treated 77 per cent, the 50 mg. Chlorpromazine treated 79 per cent, the cooled and 5 mg. Chlorpromazine-treated 72 per cent, and the cooled and 50

TABLE I. *Experimental Hemorrhagic Shock*

	Initial Blood Pressure mm. Hg.	Time to Reach Maximum Bleeding Volume	Maximum Bleeding Volume cc./Kg.
Control	93	1 hr.	51.8
Hypothermia	94	1 hr. 18 min.	51.4
Chlorpromazine 50 mg.	80	3 hr. 24 min.	41.1
Chlorpromazine 5 mg.	84	2 hr. 24 min.	52.1
Hypothermia + Chlorpromazine 50 mg.	73	3 hr. 51 min.	42.4
Hypothermia + Chlorpromazine 5 mg.	90	2 hr. 32 min.	53.5

mg. Chlorpromazine-treated were 80.3 per cent. This may be considered a further reflection of compensation to hypotension without necessity for replacement.

Additional support of tolerance is manifested by the average duration of hypotension, including the animals that were arbitrarily terminated at eight hours. The average period of hypotension for the control dogs was 3 hours 54 minutes; for the hypothermic animals 5 hours; for the 5 mg. Chlorpromazine-treated, 6 hours, 6 minutes; for the 50 mg. Chlorpromazine-treated 6 hours, 54 minutes; for the 5 mg. Chlorpromazine and hypothermia group, 6 hours, 26 minutes; and for the 50 mg. Chlorpromazine and cooled group, 7 hours, 36 minutes (Fig. 4).

These results are affected by an uncontrollable variable in the experiment that two of the five forms of therapy produced. The amount of blood lost was essentially the same for the hypothermic, 5 mg. Chlorpromazine-treated and control dogs, but it was greatly reduced in those receiving the autonomic blocking agent in large doses, either alone or when combined with surface cooling (Table I). Also notable is the decreased rapidity of the blood loss in the dogs receiving the drug in large doses (Table I). This decrease in amount and rapidity of bleeding in these animals may be a reflection of the initial hypotension. The average blood pressure at the beginning of the experiment was 93 mm. Hg. in the control dogs; 94 mm. Hg. in the hypothermic dogs; 84 mm. in the 5 mg. Chlorpromazine-treated; 90 mm. in the 5 mg. Chlorpromazine and cooled group and 73 and 80 mm. Hg. respectively, in the group receiving the larger dosage of drug alone or in combination. The better survival rates in the 50 mg. Chlorpromazine and cooled dogs as compared with those receiving the drug in large dosage alone is not entirely explained on this basis; for despite the lower initial blood pressure, both groups were bled almost identical amounts, and in essentially the same period of time. This would suggest an actual augmentation of effect when surface cooling was combined with the drug. Other workers have pointed out the apparent better tolerance of the organism to hypotension produced by sympathectomy, anesthesia or autonomic blocking agents than to hypotension mediated entirely by acute hypovolemia, and perhaps the beneficial effects reflect a lesser volume of the hemorrhage.[34] This does not mean that the drug in large dosage had no beneficial effect on the shock experiment, but the results must be cautiously interpreted. Hypothermia and the smaller dosage of drug, however, augment compensation in another fashion, since the volume and rapidity of loss of blood in these animals closely approximated those of the controls.

DISCUSSION

The hemorrhagic shock preparation used in this experiment is fairly well standardized and has been uniformly associated with a high mortality in previous studies, both in our laboratory and by other workers. Accordingly, it offers an excellent method of controlled evaluation of the various therapeutic factors employed in "artificial hibernation." Although there are numerous reports of the clinical application of hibernation to a wide variety of situations in which shock is believed to be affected beneficially, there is a paucity of data on its use under controlled experimental conditions. Jaulmes

et al.,[40] employing Wigger's method of inducing hemorrhagic shock, demonstrated an apparent protective action, but no attempt was made to ascertain the action of the individual factors, since both drugs and cooling were applied to the small number of dogs employed.

This study tends to support the concept that artificial hibernation does offer some protective action against "irreversibility" in experimental hemorrhagic shock, although the results should be interpreted cautiously. Whether applied separately or in combination, surface cooling and Chlorpromazine produced a significantly beneficial effect upon the course of the shock, but the significance and mechanism of this alteration are not entirely clear.

Surface cooling preceding bleeding significantly increases survival, and suggests an increased tolerance to shock as manifest by tolerance to the hypotension and blood lost. Approximately one-fourth of the animals were apparently compensated at the end of the eight hours, and at termination had required only moderate replacement of blood for maintenance of compensation. These observations are perhaps the most significant of this study, since they most closely parallel the control animals in the amount and rapidity of the blood lost, and would indicate a variation in the animals' resistance to "irreversibility" rather than a variation in the experiment.

That cooling might be beneficial in shock was suggested much earlier than current interest would indicate, for it has been noted by several observers that animals subjected to burn, epinephrine drip, tourniquet release, and hemorrhagic shock demonstrated much greater resistance when the environmental temperature of the laboratory was low.[1, 5, 12, 28, 42, 60, 69, 71] In his studies on the nervous system in shock, Remington[59] found that it was necessary to bleed the animals significantly more during the winter months. Allen,[1] in studies on tourniquet release shock, applied refrigeration to the constricted limb with an increase in survival of both animals and limbs, but he noted he had also inadvertently secured general body hypothermia. In comparing the effects of heat and cold in the prevention and treatment of shock, Blalock[12] found a significant increased tolerance to duration of shock when the animals were cooled but no increase in survival. Cooling was applied after shock was in progress, however, and the degree of hypothermia secured (average 25° C) without supportive measures for respiration perhaps influenced the mortality adversely. These and other studies coupled with our results perhaps do not fully support the theory advanced that hypothermia has a protective action in hemorrhagic shock but do suggest the need for further inquiry into the problem.

The mechanism involved in the beneficial effects of hypothermia is not identified in this experiment, but may be associated with one of several factors: first, it seems likely that the lowered metabolism and reduced requirements of the tissues for oxygen prevent irreparable damage to the vital centers responsible for maintenance of compensation. This is an appealing concept in that it carries prevention of peripheral stagnant anoxia further than one is able to do by correction of hypovolemia. Recent studies have demonstrated the ability of cooling to protect a variety of organs from the acute anoxia of temporary interruption of circulation.[22, 54, 55] It has been suggested, since tissue repair continues during hypothermia, that the temporary maintenance of the animal allows capillary beds damaged by anoxia to improve enough to prevent irreversibility.[12] In this regard selective cooling of viscera might add information as to the organ most responsible for maintaining compensation.

The second explanation for the beneficial effects of hypothermia is also conjectural but is based on possible alteration of effective blood flow to various body compartments during shock. Selective vasoconstric-

tion, vasodilation, or both, to organs vital to compensation may be accomplished by cooling.[3, 32, 33, 63] Aside from the known local and reflex vasomotor responses to heat and cold,[4, 56, 58] it has been demonstrated that the temperature of the blood entering and leaving different viscera varies.[36] Rodbard,[62] and D'Amato[21] and others,[65] have suggested that whole blood sequestrated in various vascular channels would account for the unexplained reduction of plasma volume that occurs in hypothermia. The close correlation of the amount and rapidity of blood lost among the controls, and among the hypothermia animals in our experiment would tend to discount involvement of any shunting mechanism.

The results obtained in animals receiving Chlorpromazine were striking, both in terms of survival, and increased tolerance to shock. This agent, however, produced an alteration in the experiment which affects comparison of these animals with the control and cooled animals. As previously indicated, the autonomolytic action of the drug, when given in massive doses, reduced the vasoconstrictive response to such an extent that bleeding was diminished in rate and volume. Survival and tolerance figures then perhaps reflect only response to lesser stress, since it changes the method to one of tolerance to hypotension rather than to blood lost. When the dosage employed was small, however, a beneficial effect was secured with no alteration in the amount of blood extracted, although it was done somewhat more slowly.

The possibility exists that Chlorpromazine possesses a pharmacologic property aside from its autonomolytic effect to account for its beneficial action, but this latter property seems to be the one of significance. Our results closely parallel those demonstrated by Remington[57-59] and others using Dibenamine, a drug with similar, but more pronounced, autonomolytic properties. When the drug was administered in doses that produced partial vasoplegia but still allowed some vasoconstrictive response to bleeding, Remington was able to reduce significantly the mortality of hemorrhagic and traumatic shock.[58, 59] The noteworthy feature of these experiments is the ability to extract from the treated animals the same volume of blood as from the controls. The autonomolytic drug employed in this study, when used in small doses, seems to add support to his interesting findings. It had been previously demonstrated that ether and spinal anesthesia, ergotamine and other autonomyltic drugs, as well as surgical sympathectomy, permit tolerance to the hypotension that accompaneis bleeding but reduce the tolerance to amount of blood lost.[31, 48, 52] Fine[29] has apparently been unable to secure a protective action with Dibenamine in the method employed in this study, but perhaps the dosage employed was excessive, as was the case in some of Wiggers' animals.[72]

The combined use of hypothermia and Chlorpromazine, simulating in the experimental animal the therapeutic regimen of "artificial hibernation" used clinically, produced striking results in regard to survival when compared with those secured from their separate application. This study suggests that the benefits are derived largely from the autonomolytic action of the drug employed since the bleeding volumes and tolerance to hypotension so closely parallel the drug treated dogs although the cumulative improvement due to the cooling cannot be excluded. When given in combination, administration of small doses of the drug seems as efficacious as larger dosage in improving tolerance to duration of hypotension, and nearly as effective in the improvement of survival. This improvement occurs with a minimal alteration in the experiment that the vasoplegic effect of the drug in large doses produces.

SUMMARY

In an attempt to determine the effect of the various factors employed in "artificial

hibernation," namely hypothermia and the administration of Chlorpromazine, on shock, these factors were applied separately and in combination to dogs subjected to "irreversible hemorrhagic shock" by the technic of Fine.

Two hundred and thirteen dogs were divided into five groups. Fifty animals served as controls; 46 were cooled to 31° C. before shock was induced; 45 and 20, respectively, were initially treated with 50 and 5 mg. of Chlorpromazine, and in 38 and 14 hypothermia was combined with 50 and 5 mg. of Chlorpromazine, respectively.

Both immediate and ultimate survival were significantly improved by administration of all the listed factors, either separately or in the various combinations. The drug in large dosage combined with hypothermia proved the most effective. A protective mechanism was also suggested by the increased tolerance to hypotension in the treated animals. This improvement was noted both in terms of hypotension time and in the number of animals which were still compensated after eight hours of shock when the experiment was arbitrarily terminated. Combination of the drug, in either small or large dosage, with hypothermia proved to be most effective therapy.

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